53 52 (Amended) A method of analyzing cellular specimens, comprising:

providing cellular specimens in a matrix, with the specimens positioned at predetermined known positions, such that when multiple copies of the matrix are provided, a two dimensional array of specimens is presented on each copy, with each specimen at a predetermined position in the matrix, and wherein each matrix has a third dimension so that when sequential copies of the matrix are provided, the specimens maintain a predetermined relationship in the array; and

exposing sequential copies of the matrix to an agent which interacts with the specimens of the array, to identify those specimens which share a common biological property.

Remarks

The Office Action mailed June 6, 2002, has been reviewed and carefully considered. Applicants thank Examiner Chakrabarti for the courtesy extended during the interview of July 30, 2002. Claims 23 and 80-85, which are subject to a restriction requirement, have been cancelled. Claim 79 has also been cancelled. Independent claim 53 has been amended to clarify that it relates to a method of analyzing cellular specimens. Entry of these amendments is respectfully requested since they do not raise any new matters and place the application in better condition for allowance.

Restriction Requirement under 35 U.S.C. §§121 and 372

The non-final Office Action mailed on December 5, 2001, set forth a restriction requirement between the following groups of claims: Group I (1-22 and 24-52); Group II (23); and Group III (53-79); and Group IV (80-85). The Office Action mailed June 6, 2002, did not mention the restriction requirement, but applicants assume that the restriction requirement has not been withdrawn. In order to expedite prosecution of the present application, claim 23 of Group II and claims 80-85 of Group IV have been cancelled. Claim 53 has been amended to clarify that it relates to a method of analyzing cellular specimens, which is similar to methods recited in the claims of Group I. Thus, the claims of Group I and Group III share a corresponding technical feature. Moreover, it is respectfully submitted that there is a single general inventive concept since the subject matter of claim 1 is not anticipated by Stapleton et al.

as explained below.

Rejection under 35 U.S.C. § 102(e)

Claims 1, 3, 4, 10-15, 24-29, 32-52, 87, 88 and 91-92 stand rejected under 35 U.S.C. § 102(e) in view of Stapleton et al. Applicants continue to maintain that Stapleton et al. is not entitled to an effective reference date that is prior to the effective priority date of the present application with respect to at least claims 1-22, 29, 49-52, 87, 88 and 91-92 for the reasons set forth in applicants' April 4th reply. Applicants also reiterate that the subject matter recited in claims 24-28 and 32-49 is not disclosed in Stapleton et al. Furthermore, even assuming *arguendo* that Stapleton et al. is available as a reference, Stapleton et al. does not disclose all the features recited in claim 1.

A. The Stapleton et al. patent does not disclose all the features recited in claims 1, 3, 4, 10-15, 24-29, 32-52, 87, 88 and 91-92

Claim 1 of the present application recites a method that includes "obtaining a plurality of donor specimens, and placing each donor specimen in an assigned location in a recipient array" (emphasis added). During the telephone interview of July 30th, Examiner Chakrabarti explained that he characterized the fibrous matrix material of Stapleton et al. as constituting a "recipient array." The spotting of a plurality of cells of the same type onto a fibrous matrix (column 22, lines 42-45) constitutes "obtaining a plurality of donor specimens" that are each placed in a recipient array according to Examiner Chakrabarti. However, applicants' representative pointed out that Stapleton et al. fails to disclose placing each individual cell (i.e., a donor specimen per Examiner Chakrabarti) in an "assigned location" on the matrix material. Indeed, in the spotting methodology of Stapleton et al. applicants cannot even conceive how it would be possible to assign each cell to a specific location.

Claim 1 also includes "obtaining a plurality of substantial copies of the recipient array in a manner that each substantial copy contains a plurality of donor specimens that maintain their assigned locations" (emphasis added). Stapleton et al. does not describe obtaining substantial copies of the matrix material that has been spotted with the cellular specimen, much less making

such substantial copies in a manner that maintains the location of each cell.

Since claim 1 is not anticipated by Stapleton et al., it follows that claims 3, 4, 10-15, 29, 43-52, and claim 87, which depend from claim 1, are likewise not anticipated.

The method recited in independent claim 88, similar to claim 1, includes "placing each donor specimen in an assigned location in a recipient array." Accordingly, Stapleton et al. also does not anticipate claim 88 or claims 91 and 92 that depend from claim 88.

Applicants also re-emphasize from their April 4th reply that Stapleton et al. does not disclose the subject matter presently recited in claims 24 and 32. Claim 24 includes "using a nucleic acid microarray to identify a biomarker to be used in a biological analysis on the recipient array." Claim 32 is directed to combining nucleic acid array techniques with biological specimen array techniques to obtain high-throughput efficiencies. In particular, a nucleic acid array technique can be used to screen multiple genes in a biological specimen to focus selection of a nucleic acid probe that is particularly promising for then screening multiple biological specimens using biological specimen array techniques. Alternatively to (or in conjunction with) such an approach, a biological specimen array technique can be used to screen multiple biological specimens to focus selection of a nucleic acid array that is particularly promising for detecting which genes are abnormally expressed. Both claims 24 and 32 employ nucleic acid arrays. The final Office Action continues to cite example 5 of the Stapleton et al. patent, as describing the method of claim 32, despite the fact that example 5 does not employ a nucleic acid array as explained in applicants' April 4th reply. The "Response to Arguments" section of the final Office Action does not contain a reply to applicants' argument regarding claims 24 and 32, much less point to exactly where a nucleic acid array is employed in example 5.

It appears that the only mention in Stapleton et al. of any tool even approaching a nucleic acid array is at column 16, lines 14-22. According to this passage, "[i]n order to detect multiple mutations from the same sample [that has been immobilized on a fibrous matrix material], it is possible to use a probe array representing different sequence combinations to which the complementary nucleic acids of the amplified product bind upon diffusing from the immobilized cells." Stapleton et al. does not describe any further use of the probe array other than detecting mutations from a single sample. Applicants, on the other hand, have recognized that nucleic acid arrays can identify a biomarker for use in the biological analysis of claim 1 (i.e., claim 24) or select the nucleic acid probe to screen multiple biological specimens in a biological specimen

array (i.e., claim 32).

B. The Stapleton et al. patent is not available as a reference against at least claims 1, 3, 4, 10-15, 29, 49-52, 87, 88 and 91-92

As explained in applicants' April 4th reply, claims 1, 3, 4, 10-15, 29 and 49-52 are entitled to priority of U.S. Provisional Application No. 60/075,979 (referred to herein as the '979 priority application). In addition, the subject matter of claims 87-94 that were added in applicants' April 4th reply is also disclosed in the '979 priority application, and thus claims 87-94 are entitled to the benefit of the priority date of the '979 priority application. Support for the added claims is found in the '979 priority application as follows: claim 87 at page 10, lines 12-21; claim 88 in originally filed claim 1 of the '979 priority application; claim 89 at page 13, lines 16-22; claim 90 at page 12, line 30 – page 13, line 15; claims 91 and 93 at page 9, line 30 – page 10, line 6; and claims 92 and 94 at page 18, lines 3-6.

Since only the Stapleton et al. provisional application filing date (April 14, 1997) is earlier than the February 25, 1998 filing date of the '979 priority application, applicants have focused on whether the Stapleton et al. provisional application satisfies the requirements of a § 102(e) reference. Pursuant to Examiner Chakrabarti's request during the July 30th interview, another copy of the Stapleton et al. provisional application is appended herewith as Exhibit A.

According to MPEP § 2136.03(IV), "in order to carry back the 35 U.S.C. 102(e) critical date of the U.S. patent reference to the filing date of a parent application, the parent application must (A) have a right of priority to the earlier date under 35 U.S.C. 120 and (B) support the invention claimed as required by 35 U.S.C. 112, first paragraph" (emphasis added). Applicants' April 4th reply pointed out that the Stapleton provisional application does not disclose the invention claimed in the Stapleton et al. patent as required under § 112, first paragraph.

In particular, the device of claim 1 of the Stapleton et al. patent requires matrix immobilization of cells and viruses present in a biological specimen "wherein the nucleic acids of cells and viruses immobilized on said matrix are detectable for the comparison of particular nucleic acid sequences in said biological specimen with another biological specimen." The Stapleton provisional application does not appear to disclose comparing the nucleic acid sequences in one biological specimen to those of another biological specimen. Detecting nucleic

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acid sequences in a single biological specimen is disclosed in the Stapleton provisional application, but there is no mention of comparing the detected sequences to other sequences from a different biological specimen.

The "Response to Arguments" section of the final Office Action does not contain a reply to applicants' argument that the Stapleton provisional application fails to meet the requirements of 35 U.S.C. § 112, first paragraph for claim 1 in the Stapleton et al. patent. If the PTO persists in applying Stapleton et al. as a § 102(e) reference against the present application, applicants respectfully request that the PTO point with specificity to, and explain how, the disclosure in the Stapleton provisional application satisfies § 112, first paragraph.

In addition, applicants also argued in their April 4th reply that the disclosure in the Stapleton et al. patent cited by the PTO as describing the subject matter of claim 1 is not present in the Stapleton provisional application. Specifically missing from the Stapleton provisional application are column 14, lines 55-66, Figure 2, the Abstract, and claim 1. In reply, the PTO states on page 12 of the final Office Action that these missing disclosures are found in the provisional application as follows: Figure 2 is described in Example 3; column 14, lines 55-66 is described on page 12, first paragraph; and claim 1 and the Abstract are described on page 11. Applicants have perused the cited portions of the Stapleton provisional application, but are unable to discern the disclosure of the portions missing from the Stapleton et al. patent.

For example, Figure 2 of the Stapleton et al. patent shows a device that includes a plurality of matrices **12'** disposed at a distal end of a plastic sheet handle **14'** that are joined together via a spline **20**. Page 20, lines 7-11, of the Stapleton provisional application describe adhering squares of the matrix material to same-sized pieces of polycarbonate film, but there is no indication that a plurality of matrices could be disposed on a single device.

Column 14, lines 55-66, describe the spacing between the matrices **12'** included in the device of Figure 2, and state that the matrices can be aligned to collect multiple samples of the same specimen. The first paragraph of page 12 of the Stapleton provisional application is completely devoid of any disclosure even remotely describing spacing between matrices or collecting multiple samples of the same specimen.

Claim 1 of the Stapleton et al. patent includes the limitation that "the nucleic acids of cell and viruses immobilized on said matrix are detectable for the comparison of particular nucleic acid sequences in said biological specimen with another biological specimen." The Abstract of

the Stapleton et al. patent describes a similar specimen comparison. Page 11, lines 11-12, of the Stapleton provisional application do state that "[t]he matrix containing the selected cellular specimen may be dried and analyzed for specific RNA and DNA content," but there is no disclosure of specimen comparison as recited in claim 1.

If the PTO continues to take the position that the Stapleton provisional application discloses the above-discussed missing features from the Stapleton et al. patent, applicants respectfully request that the PTO explain in more detail how these features are disclosed in the Stapleton provisional application. At the very least, the PTO should quote the specific language in the Stapleton provisional application that is alleged to correspond to the missing features. The burden is on the PTO to establish that the Stapleton provisional application sufficiently supports the Stapleton et al. patent as a § 102(e) reference, and not on the applicants to prove that such support is absent.

Rejections under 35 U.S.C. § 103

Claims 1-22, 24-30, 32-52, 87, 88, and 90-94 have been rejected under § 103 over Stapleton et al. in view of Furmanski et al. Stapleton et al. allegedly anticipates claims 1, 3, 4, 10-15, 24-29, 32-52, 87, 88 and 91-92, and the final Office Action does not explain why Stapleton et al. combined with Furmanski et al. would also have rendered these claims obvious. Accordingly, applicants understand the § 103 rejection to be directed at claims 2, 5-9, 16-22, 30, 90 and 94.

Stapleton et al. is not available as a reference against claims 2, 5-9, 16-22, 90 and 94 as explained above and in applicants' April 4th reply. Thus, the Stapleton et al. patent cannot be used to support a § 103 rejection of claims 2, 5-9, 16-22, 90 and 94. Applicants also note that the disclosure in the Stapleton provisional application could not be combined with Furmanski et al. for the reasons delineated in MPEP § 2136.03(IV)'s explanation of *In re Wertheim*, 209 USPQ 554 (CCPA 1981).

Even assuming *arguendo* that the Stapleton et al. patent is available as a reference, there would have been no motivation to modify the Stapleton et al. method by incorporating certain aspects of the Furmanski et al. process. In particular, Stapleton et al. teaches away from employing an embedding medium that is sectioned to obtain cross-sections for analysis.

Independent claim 16 includes the use of two embedding media – one for the donor block and one for the recipient array – and sectioning of the recipient embedding medium. The Stapleton et al. patent teaches that the method disclosed therein is superior to methods that involve fixing a specimen in an embedding medium that is then sectioned to obtain analytical samples. Specifically, column 5, lines 39-42 of Stapleton et al. state that "[e]vidence shows that the invention provides a better environment for RNA analyses of minute biological samples than the biological specimens which are fixed or paraffin-embedded." Similarly, column 10, lines 8-12 state that "[w]ith the device of the invention, cells are collected and immobilized similarly in a monolayer-like arrangement, but by means that do not involve embedding in a liquid media phase that solidifies for microtome sectioning." A skilled artisan would not have been prompted to utilize embedding and sectioning since they would destroy the alleged advantages of the Stapleton et al. method.

The PTO has cited to the advantages of the Furmanski et al. method expressed in the patent, but did not offer any reasoning connecting these advantages to the usefulness of an embedding medium and sectioning in the Stapleton et al. method. The alleged advantages of the Furmanski et al. method are expressed in very generic terms. It is by no means apparent why a skilled artisan would have expected that the Stapleton et al. method would have been improved by selecting, and incorporating therein, only a few specific aspects from the Furmanski et al. method.

Moreover, the combination of Stapleton et al. with Furmanski et al. would not have resulted in the method presently recited in claim 16. Stapleton et al. fails to teach the other features of claim 16 in addition to those absent features recognized by the PTO on page 6 of the final Office Action. In particular, Stapleton et al. does not contemplate performing a different biological analysis of array cross-sections, and comparing the results of such analysis in corresponding assigned locations of different sections to determine the existence of any correlations. It follows that Stapleton et al. does not, in fact, disclose a parallel analysis method similar to that recited in claim 16. Furmanski et al. also does not teach such a parallel analysis method, and thus the combination of Stapleton et al. and Furmanski et al. would not have produced the method recited in claim 16.

For the foregoing reasons alone, the pending § 103 rejection of claim 16 (and claims 17-22, 93 and 94 that depend therefrom) should be reconsidered and withdrawn. In addition, upon a

closer inspection of Furmanski et al., it is apparent that this patent does not actually teach all the steps cited by the PTO as supporting the § 103 rejection. Specifically, the Furmanski et al. method lacks a step of "boring receptacle cores from a recipient embedding medium to form an array of elongated receptacles." According to the Furmanski et al. method, the donor specimens are arranged in a straw that "is then placed upright into a suitable holding means, such as an embedding base mold containing a drop of molten paraffin" (column 5, lines 45-47). "Additional paraffin is then added to the strawcontaining (sp) embedding molds", and "[t]hereafter, the straw casing is removed, leaving behind a solid paraffin plug containing the multiple tissue cores" (column 5, line 64 – column 6, line 5). In other words, in the Furmanski et al. method the embedding medium is molded around the pre-placed straws instead of boring cores in a pre-existing embedding medium.

With respect to claim 30, the Examiner has not indicated where Stapleton et al. or Furmanski et al. describe or teach comparing the results of multiple immunologic analyses to determine alteration of protein expression.

Claims 1, 3, 4, 10-15, 24-29, 31-52, 87, 88, 91 and 92 have been rejected under § 103 over Stapleton et al. combined with Leveen et al. Stapleton et al. allegedly anticipates the subject matter of claims 1, 3, 4, 10-15, 24-29, 32-52, 87, 88, 91 and 92 and the final Office Action does not explain why Stapleton et al. combined with Leveen et al. also would have rendered these claims obvious. Accordingly, applicants understand the § 103 rejection over Stapleton et al. combined with Leveen et al. to be directed at claim 31.

As explained in applicants' April 4th reply, claim 31 specifies that one gene alteration of interest is an overexpression of PDGFB in breast, lung, colon, testicular, endometrial or bladder cancer. The work of Leveen et al. involved examining the expression of PDGFB in a melanoma cell line. The article does state that "many human tumor cell types frequently express PDGFA and PDGFB mRNA and protein" but there is no mention of any specific type of human cell other than melanoma. Melanoma is very different from the cancers listed in claim 31. Expression of a growth factor in melanoma is not predictive of expression in other cancers. In fact, it is known that different growth factors are expressed in different cancers. Thus, there is nothing in Leveen et al. that would have suggested searching for an overexpression of PDGFB in breast, lung, colon, testicular, endometrial or bladder cancer. If the PTO persists in maintaining this rejection, applicants respectfully ask that the PTO explain why Leveen et al. would have

specifically suggested searching for an overexpression of PDGFB in breast, lung, colon, testicular, endometrial or bladder cancer, as claimed.

Claims 1, 3, 4, 10-15, 24-29, 32-52, 86-88, 91 and 92 have been rejected under § 103 over Stapleton et al. combined with Sidransky. Stapleton et al. allegedly anticipates the subject matter of claims 1, 3, 4, 10-15, 24-29, 32-52, 87, 88, 91 and 92 and the final Office Action does not explain why Stapleton et al. combined with Sidransky also would have rendered these claims obvious. Accordingly, applicants understand the § 103 rejection over Stapleton et al. combined with Sidransky to be directed at claim 86.

Sidransky is relied upon only for teaching a method for detecting transitional cell carcinoma of the bladder, and thus does not cure any of the above-noted fatal deficiencies of the primary reference. The § 103 rejection of claim 86 should be reconsidered and withdrawn.

Claims 1, 3, 4, 10-15, 24-29, 32-52, 87-89, 91 and 92 have been rejected under § 103 over Stapleton et al. combined with Ertel. Stapleton et al. allegedly anticipates the subject matter of claims 1, 3, 4, 10-15, 24-29, 32-52, 87, 88, 91 and 92 and the final Office Action does not explain why Stapleton et al. combined with Ertel also would have rendered these claims obvious. Accordingly, applicants understand the § 103 rejection over Stapleton et al. combined with Ertel to be directed at claim 89.

Claim 89 recites an enhancement of the biological analysis method of claim 1 that involves correlating patient demographics, clinical tumor staging data, and/or patient follow-up data with the biological analysis correlation. Ertel relates to a computerized method for storing and using patient data required for hospital payment claims. The passage from Ertel cited by the PTO simply discloses a software program that can store patient demographic data together with diagnoses. It has no relevance to a biological analysis method, and certainly would not have prompted one to enhance a biological analysis technique. Since Ertel fails to teach any biological analysis method, the obviousness rejection of claim 89 over Stapleton et al. with Ertel cannot stand.

Conclusion

It is respectfully submitted that the present claims are in condition for allowance. In particular, the § 102(e) and § 103 rejections should be withdrawn since Stapleton et al. either is

not available as a reference or it fails to teach the claimed subject matter either alone or in combination with the other relied upon documents. Should there be any questions regarding this application, Examiner Chakrabarti is invited to contact the undersigned or Wayne W. Rupert at the telephone number shown below.

Respectfully submitted,

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Marked-up Version of Amended Claims
Pursuant to 37 C.F.R. §§ 1.121(b)-(c)

In the claims:

Claim 53 has been amended as follows:

53 (Amended) A method of [constructing a specimen array] analyzing cellular specimens, comprising:

providing cellular specimens in a matrix, with the specimens positioned at predetermined known positions, such that when multiple copies of the matrix are provided, a two dimensional array of specimens is presented on each copy, with each specimen at a predetermined position in the matrix, and wherein each matrix has a third dimension so that when sequential copies of the matrix are provided, the specimens maintain a predetermined relationship in the array; and

exposing sequential copies of the matrix to an agent which interacts with the specimens of the array, to identify those specimens which share a common biological property.